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REVIEW

Herpes Zoster and COVID-19 Vaccination: A Narrative Review

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Abstract: COVID-19 was a worldwide emergency, leading to a global health crisis, which completely revolutionized every aspect of human life. Several strategies were adopted to limit the spreading of the infection such as testing and contact tracing, quarantine and isolation, use of face mask, social distancing, lockdowns, travel restrictions, etc. Of these, vaccines were the most important measures to reduce the transmission of the virus and the severity of the infection, in order to overcome the pandemic. Fortunately, vaccination campaign was a success, showing to be efficient in controlling and preventing the COVID-19, reducing the risk of disease progression, hospitalization, and mortality. Monitoring and addressing vaccine-related adverse events have been essential for maintaining public confidence. Indeed, with the increasing number of vaccines administered, various cutaneous reactions have been reported, making dermatologists key players in their recognition and treatment. Particularly, several cutaneous diseases and cutaneous findings have been reported. Of note, also viral reactivations have been described following COVID-19 vaccination. Among these, varicella zoster virus (VZV) reactivation has been collected. Globally, an early diagnosis and an accurate treatment of herpes zoster (HZ) is mandatory to reduce possible complications. In this context, we conducted a review of the current literature investigating cases HZ following COVID-19 vaccination with the aim of understanding the possible causal correlation and underlying pathogenetic mechanisms to offer clinicians a wide perspective on VZV reactivation and COVID-19 vaccines.

Keywords: COVID-19, vaccination, herpes zoster, safety

Introduction

In late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), started to spread around the world, becoming a worldwide emergency and leading to a global health crisis, which completely revolutionized every aspect of human life.[1–3] Several strategies were adopted to limit the spreading of the infection such as testing and contact tracing, quarantine and isolation, use of face mask, social distancing, lockdowns, travel restrictions, public health messages, hygiene measures, international cooperation, and vaccination campaign.[4–6]

Of these, vaccines were the most important measures to reduce the transmission of the virus and the severity of the infection, in order to overcome the pandemic.[7] Currently, 4 vaccines have been licensed by the European Medicines Agency (EMA), with two different mechanisms of action: viral-vector-based vaccines (AstraZeneca; AZD1222 and Johnson & Johnson; Ad26.COV2.) and mRNA-based vaccines (Pfizer/BioNTech; BNT162b2 and Moderna; mRNA-1273).[7] Moreover, several vaccines have been authorized in other countries such as "Sputnik V" (Gamaleya Research Institute), "Convidecia" (CanSino Biologics), and "CoronaVac" (Sinovac).[7] However, also vaccination campaign was a global challenge due to several concerns raised by vaccines themselves.[8–10] First of all, there were logistic concerns (vaccine supply and distribution, production capacity, equitable access, infrastructure and healthcare workforce, logistical challenges, public communication, legal and regulatory challenges, etc.).[8,9] Secondly, vaccination campaign was also limited by vaccine hesitancy, often due to misinformation and mistrust of vaccination related to the rapidity of production

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of vaccines and the mechanism of action, particularly mRNA based.[8,9] Fortunately, the initial doubts about vaccines were overcome as well as logistic concerns were solved.[8,9,11] On consequence, vaccination campaign was a success, showing to be efficient in controlling and preventing the COVID-19 pandemic, reducing the risk of disease progression, hospitalization, and mortality.[8,9]

In this scenario, monitoring and addressing vaccine-related adverse events (AEs) have been essential for maintaining public confidence.[12,13] As regards the dermatological field, with the increasing number of vaccines administered, various cutaneous reactions have been reported, making dermatologists key players in their recognition and treatment.[14–20] Particularly, several cutaneous diseases (eg, psoriasis, lichen planus, hidradenitis suppurativa, bullous diseases, etc.) and cutaneous findings (eg, maculopapular, urticarial, vesicular rashes, etc.) have been reported.[21–23] However, the clinical significance of these reactions, and the possible pathogenetic mechanisms, is still unknown, as well as it should be noted that in the majority of cases, these reactions were self-resolving or limited to a few days.[21–23] Of note, also viral reactivations have been described following COVID-19 vaccination. Among these, varicella zoster virus (VZV) reactivation has been collected. VZV is a complex medical condition that may involve infectiology, dermatology, and neurology, making its treatment challenging.[24–26] While varicella is caused by acute viremia, herpes zoster (HZ) is caused by viral reactivation, typically involving a single dermatome and presenting as burning or pain followed by a cutaneous eruption with multiple umbilicated and painful vesicles.[27] The exact triggers for reactivation are not fully understood but may involve a weakened immune system, aging, or stress.[27] Moreover, HZ infection may be complicated by postherpetic neuralgia, secondary bacterial infection, or ophthalmic complications.[27] Thus, an early diagnosis and an accurate treatment are mandatory.[27] In this context, we conducted a review of the current literature investigating cases HZ following COVID-19 vaccination with the aim of understanding the possible causal correlation and underlying pathogenetic mechanisms to offer clinicians a wide perspective on VZV reactivation and COVID-19 vaccines.

Materials and Methods

For this review manuscript, a comprehensive literature search was performed by using several databases (Embase, MEDLINE, EBSCO, PubMed, Google Scholar, and the Cochrane Skin), up until September 19, 2023. The following terms were searched and matched to find relevant manuscripts: “COVID-19”, “SARS-Coronavirus-2”, “SARS-CoV-2”; “cutaneous disease”, “cutaneous reactions”, “adverse events”, “BNT162b2”, “side effects”, “mRNA”, “AZD1222”, “viral-vector”, “mRNA-1273”, “Johnson & Johnson”, “Pfizer/BioNTech”, “Moderna”, “Ad26.COV2.S”, “AstraZeneca”, “vaccine”, “vaccination”, “efficacy”, “safety”, “herpes zoster”. The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines were followed to point out relevant data from the screened and analyzed articles.[28] Moreover, only English language manuscripts were considered. Furthermore, the abstracts and the texts of designated articles were reviewed to refine the research as well as references were also considered to avoid that some manuscripts could be missed. Exclusion criteria include: non-English manuscripts, article regarding other viral reactivations or non-involving vaccines approved by EMA. This manuscript is based on previously performed studies and does not contain any studies with human or animals participants carried out by any of the authors.

Results

A total of 76 records were found from the investigated databases. However, only 72 manuscripts were assessed for eligibility, since duplicate manuscripts and articles non-respecting study were excluded. Finally, 31 manuscripts were selected at the end of the literature research for our review.[29–60]

The results have been summarized in Table 1.

Globally, 4555 cases of HZ following COVID-19 vaccinations were found. Among these, the largest number of cases has been reported by Florea et al in a cohort study investigating the association between mRNA COVID-19 vaccination and subsequent HZ development within 90 days from vaccination.[29] Cohort included: mRNA-1273 recipients (n = 1.052.362), BNT162b2 recipients (n = 1.055.461), and comparators (n = 1.020.334).[29] The authors showed and adjusted hazard ratio (aHR) for HZ up to 90 days following the second dose of mRNA-1273 and BNT162b2 of 1.14 (1.05–1.24) and 1.12 (1.03–1.22), respectively.[29] Moreover, an aHR of 1.18 (1.06–1.33) and 1.15 (1.02–1.29) was found in patients aged ≥50 years after the second dose of mRNA-1273 and BNT162b2 vaccine as compared with unvaccinated subjects.[29]

Table 1 Varicella Zoster Virus Reactivation After COVID-19 Vaccine

Authors	Country	Cases	Vaccines	Time	Dose
Florea et al[29]	US	2797	BNT162b2: 1313 mRNA-1273: 1484	Maximum 90 days	First dose: 0 Second dose: 2797
Birabaharan et al[41]	US	1228	BNT162b2: NR mRNA-1273: NR	Maximum 28 days	NR
Barda et al[30]	US	283	BNT162b2: 283	Maximum 42 days	NR
Akpandak et al[52]	US	45	BNT162b2: NR mRNA-1273: NR Ad26.COV2: NR	Medium: 12 days	NR
Català et al[55]	Spain	41	BNT162b2: 28 mRNA-1273: 6 AZD1222:7	Medium: 4.6 days	NR
Fathy et al[56]	US	35	BNT162b2: 19 mRNA-1273: 16	Medium: 7 days	First dose: 27 Second dose: 18
Naoum et al[57]	German	22	BNT162b2: 16 mRNA-1273: 5 AZD1222:1	Medium: 10 days	First dose: 13 Second dose: 9
Lee et al[58]	US	20	BNT162b2: 6 mRNA-1273: 14	Medium: 3–38 days	First dose: 15 Second dose: 5
Lee et al[59]	Korea	14	BNT162b2: 5 mRNA-1273: 5 AZD1222: 4	Days 1–21: 9 Days 22–42: 5	First dose: 4 Second dose: 10
McMahon et al[60]	US	10	BNT162b2: 5 mRNA-1273: 5	Medium: 7 days	First dose: 6 Second dose: 4
Monastirli et al[31]	Greece	7	BNT162b2: 7	NR	First dose: 4 Second dose: 3
Psichogiou et al[32]	Greece	7	BNT162b2: 7	Medium: 9 days	First dose: 5 Second dose: 2
Furer et al[33]	Israel	6	BNT162b2: 6	Medium: 3–14 days	First dose: 5 Second dose: 1
Rodríguez-Jiménez et al[34]	Spain	5	BNT162b2: 5	Medium: 1–16 days	First dose: 5 Second dose: 0
Alpalhão et al[35]	Portugal	4	BNT162b2: 2 AZD1222:2	Medium: 3–6 days	First dose: 4 Second dose: 0
Chiu et al[36]	Taiwan	3	mRNA-1273: 1 AZD1222:2	Medium: 2–7 days	First dose: 3 Second dose: 0
Jiang et al[37]	Taiwan	3	AZD1222: 3	Medium: 3–7 days	NR
Lazzaro et al[38]	US	3	BNT162b2: 3	Maximum: 14 days	First dose: 3 Second dose: 0
Mohta et al[39]	India	3	AZD1222: 3	Maximum: 7 days	First dose: 3 Second dose: 0

(*Continued*)

Table 1 (Continued).

Authors	Country	Cases	Vaccines	Time	Dose
Vastarella et al[40]	Italy	3	AZD1222:3	Medium: 6–10 days	First dose: 3 Second dose: 0
Özdemir et al[42]	Turkey	2	AZD1222: 2	Medium: 1–2 days	First dose: 2 Second dose: 0
Palanivel[43]	India	2	AZD1222:2	Medium: 4–7 days	First dose: 2 Second dose: 0
Rehman et al[44]	India	2	AZD1222: 2	Medium: 3–28 days	NR
Toscani et al[45]	Italy	2	BNT162b2: 2	Medium: 2–24 days	First dose: 0 Second dose: 2
Aksu et al[46]	Turkey	1	BNT162b2: 1	Medium: 5 days	First dose: 0 Second dose: 1
Ardalan et al[47]	Iran	1	AZD1222:1	Medium: 2 days	First dose: 1 Second dose: 0
Channa et al[48]	US	1	mRNA-1273: 1	Medium: 3 days	First dose: 0 Second dose: 1
David et al[49]	US	1	mRNA-1273: 1	Medium: 8 days	First dose: 1 Second dose: 0
Tessas et al[50]	Finland	1	BNT162b2: 1	Medium: 7 days	First dose: 1 Second dose: 0
Tripathy et al[51]	India	1	AZD1222: 1	Medium: 5 days	First dose: 1 Second dose: 0
Vallianou et al[53]	Greece	1	BNT162b2: 1	Medium: 11 days	First dose: 1 Second dose: 0
You et al[54]	Korea	1	BNT162b2: 1	Medium: 5 days	NR

In conclusion, the authors suggested an increased risk of HZ following COVID-19 vaccination, especially in patients aged ≥50 years without history of zoster vaccination.[29]

Similarly, Barda et al assessed an increased risk of VZV reactivation following COVID-19 vaccination with BNT162b2 in their cohort study involving 884,828 subjects.[30] Among these, 283 cases of HZ were collected, suggesting a positive correlation between VZV reactivation and vaccination (risk ratio, 1.43; 95% CI, 1.20 to 1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2 to 24.2).[30]

On the contrary, Birabaharan et al reported the results a cohort study enrolling 1,306,434 patients receiving at least one dose of mRNA-based COVID-19 vaccine.[41] Of these, 1.228 (0.1%) reported VZV reactivation within maximum of 28 days after vaccine. Nevertheless, a statistically significant association between HZ and COVID-19 vaccination was not found.[41] On consequence, the authors stated that COVID-19 vaccination was not associated with an increased risk of HZ.[41] The main limitation of the study was the absence of the specification of the dose and type of mRNA vaccine.[41] In line with Birabaharan et al, also Akpandak et al showed that there was not an increased risk of VZV following COVID-19 vaccination in their cohort of 1,959,157 individuals.[52] Indeed, only 45 cases were reported, allowing the authors to conclude that there was not an increased risk of HZ following vaccination with BNT162b2 (IRR = 0.90, 95% CI: 0.49–1.69, p = 0.74), mRNA-1273 (IRR = 0.74, 95% CI: 0.36–1.54, p = 0.42), or Ad26.COV2.S (IRR = 0.50, 95% CI: 0.07–2.56, p = 0.42).[52]

Globally, the remaining cases of HZ development following COVID-19 vaccination were limited to case series and case reports. Among these, it should be pointed out 6 cases of HZ in patients with autoimmune inflammatory rheumatic diseases,[31] 3 subjects with VZV meningitis complicated by enhancing nodular leptomeningeal lesions of the spinal cord and VZV ophthalmicus of the cornea and eyelid, respectively,[38] and a case of VZV reactivation in a patient previously vaccinated for VZV.[53]

Globally, the type of COVID-19 vaccination associated with HZ development was described only for 3282 out of 4555 subjects (72.1%), with BNT162b2 as the commonest (n = 1711), followed by mRNA-1273 (n = 1538), and Ad26.COV2 (n = 33). Finally, the time between vaccination and VZV development ranged from 1 to 90 days.

Discussion

COVID-19 pandemic period strongly affected daily routine. Dermatological clinical practice was strongly forced to adopt strategies to contrast the COVID-19 diffusion in order to allow patients the continuity of care.[61–64] As regards the dermatological practice, dermatologists played a key role during the pandemic making possible to allow the continuity of care for patients affected by chronic disorders requiring various treatment such as biologics,[65–71] as well as the management of skin cancers.[72–74]

Globally, among the several measures adopted to contain COVID-19 infection,[75] vaccination was the most important. The Herpesviridae family is a large family of double-stranded DNA viruses that infect a wide range of animals, including humans, characterized by their ability to establish latent infections, which means they can remain dormant in the host's cells for extended periods and reactivate later.[76–78] Three subfamilies can be distinguished: alphaherpesvirinae (herpes simplex virus type 1 and herpes simplex virus type 2, which cause oral and genital herpes, as well as varicella-zoster virus), betaherpesvirinae (cytomegalovirus, human herpesvirus 6, and human herpesvirus 7 (HHV-7)), gammaherpesvirinae (Epstein–Barr virus and Kaposi's sarcoma-associated herpesvirus). In particular, alphaherpesvirinae establishes latent infections in neurons, while betaherpesvirinae and gammaherpesvirinae establish latent infections in the immune system and in lymphocytes and epithelial cells, respectively.[76–78] These viruses can cause a wide range of diseases, from mild cold sores to severe and potentially life-threatening conditions, depending on the specific virus and the host's immune status.[76–78] Reactivation of herpesviruses (Epstein–Barr virus, cytomegalovirus and herpes simplex virus) following COVID-19 vaccination have been reported by several case reports. However, VZV reactivation is the commonest. In this context, we performed a review of the current literature to determine the correlation between the COVID-19 vaccination and VZV. Of interest, VZV reactivation was also reported following COVID-19 infection.[79]

In our review, a total of 31 manuscripts were collected, reporting 4555 cases of HZ development following COVID-19 vaccination. In particular, BNT162b2 was reported as the commonest type of vaccine associated with VZV reactivation, followed by mRNA-1273 and Ad26.COV2. However, it should be stated that BNT162b2 is the commonest type of vaccine administered. Finally, the time between vaccination and VZV development ranged from 1 to 90 days. Of interest, cases of HZ have been described following both doses of vaccinations as well as both types of mechanism of action (mRNA-based or viral-vector based) suggesting that the possible pathogenetic mechanisms are independent from the mechanism of action of vaccine. Globally, age, weakened immune system, stress, certain medical conditions, injury or trauma, are considered as possible risk factors. In theory, these conditions may lead to the reactivation of VZV.[80–85] As regards COVID-19 vaccination and HZ, the possible pathogenetic mechanism may be find in the immune imbalance related to the vaccination.[80–85] Indeed, vaccine causes CD8+ T cells reduction, increased NF-κB signaling, increase in classic monocyte contents, and reduced type I interferon responses, leading the immune system in a vulnerable state.[80–85] In particular, type I IFN receptor signaling in CD8+ T cells plays an essential role in regulating memory cell response to viral infection and blockage of reactivation.[80–85] On consequence, the alteration of this system related to COVID-19 vaccination may be the cause of VZV reactivation.[80–85] To summarize, cases of VZV reactivation have been reported also following other vaccines (such as influenza, diphtheria, tuberculosis, poliomyelitis, etc.).[80–86] It is possible that in predisposed individuals, immune dysregulations induced by vaccines may lead to viral reactivation, similar to the phenomenon of "immune reconstitution inflammatory syndrome" observed during HIV treatment.[80–85] The stimulation of the immune response and its polarization towards a specific T-cell response against a particular infectious agent (eg, a vaccine) may temporarily compromise the T-cell-mediated control of latent infections like VZV, HSV, HHV-6, and HHV-7, leading to viral reactivation.[80–85] However, the exact pathogenetic mechanism remains unknown and further studies are needed.

Moreover, it should be stated that cases of HZ following vaccination are rare, and only few complicated cases have been described, as well as the safety of vaccination has been reported also in patients undergoing biologics.[87–90] Thus,

more studies are needed to identify possible risk factors, which may increase the risk of VZV following COVID-19 vaccination as well as the protective role of VZV vaccine in order to identify "at-risk" patients. Certainly, the possibility of HZ following vaccination should be considered in order to early recognize and treat this disease.

Strengths and Limitations

The main strengths of our work were the PRISMA methods for the literature research and the number and quality of investigated articles. Indeed, our study offers a comprehensive overview of the published literature and highlights the available data with rigorous quality assessment.

Limitations of the study should also be discussed. First of all, despite all of the reported cases that have been collected in our review, the number of patients is inadequate for certainly assessing the correlation between vaccines and VZV reactivation. Second, clinical trials or comparison between vaccinated and non-vaccinated participants are lacking. Furthermore, the causal temporal correlation between COVID-19 vaccination and viral reaction cannot be ruled out in most of the cases. In addition, several viral reactivations related to COVID-19 vaccines have not been described in literature because they were mild and/or patients did not seek medical advice, leading to an underestimation of the epidemiological value of our work. Moreover, our assumptions, especially in the discussion, must be taken simply as suggestions and not as definite proposals, as our work has not had the support of meta-analysis, which may allow our results to be generalized. Finally, several cutaneous reactions related to COVID-19 vaccination were not considered in our review.[91,92]

Conclusions

COVID-19 vaccination campaign was a worldwide success. However, with the raising number of vaccinated individuals, several cutaneous reactions have been reported, which often were not collected in clinical trials. Among these, viral reactivations have been described. In our review, we focused the attention to VZV reactivation following COVID-19 vaccination, which is the commonest described viral reactivation. Fortunately, the percentage of HZ development is extremely low if compared with the number of vaccines administered as well as an increased risk of VZV reactivation following vaccination cannot be statistically demonstrated. In our opinion, clinicians should keep in mind the possibility of HZ development following vaccination to offer patients a personalized approach.[93,94] Moreover, more studies are needed to identify "at-risk" patients and adopt preventative measures. Certainly, vaccines should not be discouraged.

Disclosure

The authors report no conflicts of interest in this work.

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